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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/803,550	FOGARTY, PATRICK	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-15,17,18 and 27-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-15, 17-18, 27-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/16/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 11-15, 17-18, 27-38 are pending. Claims 1-10, 16, 19-26 are canceled. New claims 35-38 are added. Claims 11-15, 17-18, 27-38 are under consideration.

WITHDRAWN REJECTIONS

Applicant's arguments, see page 5, filed 05/04/06, with respect to rejection of claims 11-12, 27-29 and 31under 35 U.S.C. 101 have been fully considered and are persuasive. Applicants amended claims to recite "non-human" animal species. The rejection of claims 11-12, 27-29 has been withdrawn.

Applicant's arguments, see page 12, filed 05/04/06, with respect to rejection of claim 12 under 35 U.S.C. & 112 have been fully considered and are persuasive. The rejection of claim 12 has been withdrawn.

Applicant's arguments, see page 12, filed 05/04/06, with respect to rejection of claims 11-15, 17-18 under 35 U.S.C. & 102(a) have been fully considered and are persuasive. The rejection of claims 11-15, 17-18 has been withdrawn.

Applicant's arguments, see page 12, filed 05/04/06, with respect to rejection of claims 11-15, 17-18 under 35 U.S.C. & 102(b) have been fully considered and are persuasive. The rejection of claims 11-15, 17-18 has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-15, 17-18, and 27-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inserting an exogenous nucleic acid into the genome of a mouse, comprising co-introducing a first nucleic acid sequence encoding a gene of interest operably linked to a promoter, wherein said nucleic acid sequence further comprises a P-element derived recognized insertion sequences and a second nucleic acid sequence encoding a transposase into the testis of said mouse wherein first nucleic acid is inserted into the germline of said mouse and wherein said nucleic acid is transmitted to the offspring, does not reasonably provide enablement for the claimed method with respect to all other non-human and non-Drosophilidae animals and cells obtained from these animals. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claimed invention encompasses a method of inserting an exogenous nucleic acid into the genome of a non-human and non-Drosophilidae animal, comprising introducing into said animal a transposase recognized insertion sequence vector and a second vector comprising a transposase under conditions sufficient for transposition to occur and exogenous nucleic acid vector is inserted into the genome of any type of cell in the animal including germline transmission (see claims 11-14). Embodiments limit vector size range in length from about 50 to 150,000 bp, and further embodiments limit the animal species into non-human animal, non-Drosophilidae, rodent and mouse animal species. Embodiments also encompass obtaining cells from said animals which contain P-element derived transposase recognized 31 bp insertion sequences integrated into their genome. Because these claims encompass a wide range of nucleic acid conditions sufficient for transposition to occur so that the exogenous nucleic acid is inserted into the genome of non-human and non-Drosophilidae animals and phenotypes associated with it and cells obtained from said animals, the detail of the disclosure provided by the applicant, in view of the prior art, must encompass a wide knowledge, so that one of skill in the art, at the time of the invention, would be able to practice the invention as claimed by the applicant, without undue experimentation being imposed on the skilled artisan. Given the lack of guidance provided by the specification this burden has not been met because it would have require undue experimentation for one of skill in the art to produce the other species animal(s) embraced by the claims with a P-

element derived transposase recognized insertion sequences vector and a transposase vector integrated into their genome and cells obtained from said animals without reasonable expectation of success.

As a first issue, the claims are directed to a method of producing transgenic non-human and non-Drosophilidae animals expressing P-element derived recognized insertion sequences encoding a gene of interest into a cell type of said animals including the germline and a method of producing the same transgenic non-human and non-Drosophilidae animals. The specification teaches the production of transgenic mice that express P element recognized insertion sequences encoding the beta galactosidase reporter gene into every tissue examined such as testis, liver, spleen, heart, lung, brain and intestine (specification p 18-18). Specification also teaches that mating of said mice integrated vectors are heritable (specification p 19, last paragraph). However, the specification does not provide any guidance how to practice claimed method in any other non-human and non-Drosophilidae animal species other than mice. The art teaches that DNA transposons proved to be remarkably useful as transgenic vectors as well as insertional mutagens in certain invertebrate species, however, the art also teaches that a number of transposon systems require specific host proteins for transposition, which limits their mobility outside their natural hosts as noted by Izsvak et al, (p 94, 1st column and 2nd column, 2nd paragraph) (J Mol Biol 302: 93-102, 2000). Izsvak et al, noted also that there is extensive variation in the extent to which transposase stimulates integration between different species and between different cell lines of the same species (p 100, 2nd column, 2nd paragraph). This is also supported by

the art of Castro et al, where they note that the molecular mechanisms that control P element transposition and determine its tissue specificity remain incompletely understood, although much information has been compiled about this element in the last decade (Genetica, 1292): 107-18, 2004, abstract). Given the state of the art it would appear that the germline transmission of the P-derived element transposase insertion sequences vectors into the genome of any cell type including the germline is unpredictable in other non-human and non-Drosophilidae animals other than the mice as taught by the applicant. At the time of the instant invention, Plasterk et al, (TIG, 15(8): 326-332, 1999) states that transgenic technology is currently applied to several animal species of agricultural or medical importance, such as fish, cattle, mosquitoes and parasitic worms, however, the repertoire of genetic tools used for molecular analyses of mice and Drosophila is not always applicable to other species (abstract). For example, while retroviral enhancer-trap experiments in mice can be based on embryonic stem (ES) cell technology, this is not currently an option with other animals. Similarly, the germline transformation of Drosophila depends on the use of the P-element transposon, which does not jump in other species (abstract). Thus a skilled artisan would have required undue experimentation to practice claimed method as claimed in the instant application because neither the art of record nor the applicant has provided sufficient guidance to practice claimed method without a reasonable expectation of success.

As a second issue, claimed invention also encompass a method of obtaining cells from said animals which contain P-derived element transposase recognized 31 bp

insertion sequences integrated into their genome as recited in claims 27-34. However, the specification lacks to provide guidance for such claimed method in any non-human and non-Drosophilidae animal species. The specification also contemplates that the subject methods of stable integration of exogenous nucleic acid into the genome of a target animal find use include **gene therapy** (specification, p 15, lines 10-30, p 16, lines 1-2). The mere capability to perform gene therapy in any non-human and non-Drosophilidae animal species is not enabling because a desired phenotype can not be predictably achieved by simply introducing transgene P element vectors as disclosed in the specification. The art of gene therapy is unpredictable. Numerous factors complicate the gene delivery art, which would not have been shown to overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into tissues, etc), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRMA produced, the stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically on the vector being used and the protein being produced. While progress has been made in recent years for in vivo, gene transfer, vector targeting in vivo to desired organs continuous to be unpredictable and inefficient. This is supported by numerous teachings in the art. Romano et al, (Stem Cells, 18:19-20, 2000) reporting on the recent developments of gene therapy, noted, (However, the real effectiveness of gene therapy programs is still in question.

After a decade of clinical trials, the therapeutic applications of gene transfer technology are still at a rather preliminary stage" (p 19, abstract). The specification discloses that an advantage of the subject vector over other known nucleic acid vectors is that the subject vectors provide random insertion of a foreign nucleic acid, which is desirable in many applications (specification, p 22, lines 5-15). However, the art also teaches that random integration also increases the possibility of gene disruption, including disruption of genes involved in cell cycle or tumor suppression (p 105, 2nd column, 2nd paragraph, Richardson et al, Stem Cells, 20: 105-118, 2002). Even a year post filling of the instant application, Richardson et al, note delivery remains a significant hurdle irrespective of cell type and/or repair mechanisms (p 106, 2nd column, last paragraph). It is noted that these reviews by the leaders in the field of gene therapy are about those gene therapy are about those gene therapy applications where the mechanism of action and some efficacy has been determined in animal models and there may be some extrapolatable correlations indicating the therapeutic effects of a particular gene's encoded protein. In the instant case, the specification does not teach as to how a P element vector as described which have the capability to mobilize up to 150 Kb of DNA carrying a DNA sequence or of similar length with therapeutic efficacy into any target cell or tissue of any claimed non-human and non-Drosophilidae animal species. Furthermore, the specification does not provide any guidance as to what doses of a nucleic acid of subject vectors will be administered to target desired tissues or organs in any of the claimed animal species. While applicants specification supports efficient transfer of for in vivo tail vein injection or intratesticular or intramammary injection of subject vector

into mice, the specification fails teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient transfer is achieved by any route of delivery in other non-human and non-Drosophilidae animal species as claimed in the instant application. The specification merely recites that rats and fish have also been examined for the integration of the C3.1 vector and the results are as seen above, modifying the amount of DNA based on the weight of difference between animals (specification, p 19, lines 1-3). The specification fails to teach any specific targeting techniques and sufficient guidance, which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art, which would allow one of skill in the art to practice the claimed invention in non-human and non-Drosophilidae animal species other than mice without undue experimentation.

Therefore, limiting the scope of the claimed invention to a method of inserting an exogenous nucleic acid into the genome of a mouse comprising introducing into said mouse a P element transposase recognized insertion sequence vector and a second vector comprising a transposase and wherein said vectors are inserted into the genome of mouse and wherein integration occurs in every cell type, tissue type and organ examined and integrated vectors are heritable in mice.

Response to Arguments

Applicant's arguments filed 05/04/06 have been fully considered but they are not persuasive. Applicants argue that the specification clearly details the preparation and production of such transgenic animals (Remarks p 2, last paragraph). Applicants further

argue that beginning on page 10, the specification provides a detailed disclosure of how to generate such animals using the transposase recognized insertion sequence vectors and a variety of well known nucleic acids delivery techniques, as well as references describing such techniques in greater detail and working examples showing use of such vectors in generating transgenic rodents and thus the specification fully demonstrates that such non-human and non-Drosophilidae transgenic animals according to the pending claims without undue experimentation (Remarks, p 6, last paragraph).

In response this is not found persuasive because beginning on page 10 Applicants describe methods of using the subject vectors in a variety of applications in which it is desired to introduce and stably integrate an exogenous or endogenous nucleic acid into the genome of a whole animal (specification p10, last paragraph). Applicants further describe on page 11, first paragraph, that exogenous nucleic acid means a stretch of nucleotides that is not initially present in the target cell, while endogenous nucleic acid means a nucleic acid that pre-exists in the genome of the animal and in many embodiments the sequence of nucleotides present in the exogenous nucleic acid will be one that is not found in the genome of the animal and the subject methods can be used with a variety of animals. The specification has failed to provide guidance as to the sequence of nucleotides present in the exogenous nucleic acid, which will be one that is not found in the genome of the no-human and non-Drosophilidae animals. The guidance provided by the specification does not correlate to the to the use of any particular sequence nucleotides present in the exogenous nucleic acid that is not found in the genome of the non-human and non-Drosophilidae

animal species. Moreover, the working examples provided by the specification while exemplifying creation of rats and fish that for the integration of the C3.1 vector and the results are as seen in mice, modifying the amount of DNA based on the weight difference between animals (specification, p 19, lines 1-3), did not disclose what modifying amounts of DNA based on the weight difference between species were used to create the transgenic rats and fish and therefore failed to provide the skilled artisan with adequate guidance to make and use any of the transgenic non-human and non-Drosophilidae animals. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without undue experimentation.

Applicants further argue that the Applicants in citing the research publications have sought to establish that the field of generating transgenic mammalian animals is not an **unpredictable** as stated by the Examiner (Remarks, page 9, 1st paragraph). Applicants further argue that the methods disclosed in the cited references used to generate the transgenic non-human mammalian animals were not exactly the same as the method disclosed in the resent application, however, the publications have been cited to establish that by reporting the successful generation of non-human mammalian transgenic animal models the cited publications have substantiated the Applicant's position that the field is not unpredictable as asserted by the Examiner (Remarks, p 9, 2nd paragraph).

In response to Applicant's arguments this is not found persuasive because the art of making transgenic animals other than mice is unpredictable. A mere statement

that rats and fish have also been examined for the integration of the C3.1 vector and the results are as seen with mice, modifying the amount of DNA based on the weight difference between animals is not sufficient to enable the breadth of the claims as directed to transgenic non-human and non-Drosophilidae animals comprising claimed nucleic acid. If there is no disclosure of the starting material or of any conditions under which claimed process can be carried out, without undue experimentation. The specification describes that the subject vectors can be used to stably insert a wide variety of endogenous and/or exogenous nucleic acids into the genome of the whole animal and the nucleic acid is used to stably introduce the gene into the genome of the target whole animal and observe changes in the phenotype in order to characterize the gene (specification p 9, lines 4-24). One of skill in the art cannot rely on the on the transgenic art to make such transgenic animal phenotypes. The art teaches the transgenes embedded in trasposon vectors can be expressed but are also subject to position effects (Dupuy et al, (PNAS, 99(7): 4495-4499, 2002) (p 4499, 1st column, 2nd paragraph). Even after the filing of the instant application, Dupuy et al, also states that SB10-mediated transgenesis may be used to create transgenic animals in various strains of mice or in other species for which transgenesis is currently very inefficient or impossible (p 4499, 2nd column last paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27-34, rejected under 35 U.S.C. 103(a) as being unpatentable over Clough et al, (Mol Cell Biol, 5(4): 898-901, 1985) in view of Rio et al, (J Mol Biol, 200:411-415, 1998 or Cell 44: 21-32, 1986 or Rio TIG 7: 282-287, 1991).

Clough et al, teaches a gene transfer vector containing the herpes simplex virus type 1 thymidine kinase (TK) gene flanked by Drosophila P element terminal repeats (p 899, figure 1). This vector was introduced into mouse LTK-cells and enhanced the frequency of stable transformation to the TK+ phenotype by approximately 50-fold relative to a similar plasmid lacking the P element terminal repeats (p 899, Table1). At the time of the instant application an artisan of skill in the art would have been motivated to introduce this vector into mouse embryos because Clough et al, teaches this system provides means of enhancing the transfer of a variety of genes into mammalian cells of different types and into mammalian embryos (p 900, 2nd column, 1st paragraph).

The cited art does not teach that the vector further comprises sequences that encode transposase enzyme and that the transposase recognition sequences are 31 base pair long.

Both the Rio articles teach vectors that comprise P element recognition sequences flanking a sequence (J Mol Biol, p412, figure 1 and TIG, p 283). Additionally, Rio et al, teaches that P elements will be good genetic tools to use in other organisms where classical genetics is tedious. They further teach transposase activity in yeast and animal cells using an expression vector.

At the time of the invention it would have been obvious to include the transposase encoding sequences taught by Rio et al in the vector of Clough or to provide the transposase encoding sequences in a separate vector with a reasonable expectation of success. An artisan of skill would have been motivated to include transopsase coding sequences in the expression vector because this would eliminate the administration of the protein to a cell separately and introduce this vector into a mouse embryo because Clough teaches that this system provides a means of enhancing the transfer of genes into mammalian embryos.

Applicant's arguments, see page 12, filed 05/04/06, with respect to rejection of claims 27-34 under 35 U.S.C. & 103 have been fully considered and are not persuasive.

Applicants argue that, there must be some motivation (Remarks page 13).

In response, an artisan of skill would have been motivated to include transposase coding sequences in the expression vector because this would eliminate the administration of the protein to a cell separately and introduce this vector into a mouse embryo because Clough teaches that this system provides a means of enhancing the transfer of genes into mammalian embryos.

Applicants argue that, there must be a reasonable expectation of success (Remarks page 13).

In response, there is a reasonable expectation of success because Clough et al, teaches a gene transfer vector containing the herpes simplex virus type 1 thymidine kinase (TK) gene flanked by Drosophila P element terminal repeats and this vector was

introduced into mouse LTK-cells and enhanced the frequency of stable transformation to the TK+ phenotype (p 899, figure 1).

Applicants argue that the prior art reference, or references must combined, must teach or suggest all the claim limitations (Remarks page 14).

In response Clough teaches a Carnegie 4 P element plasmid containing P element transposase recognized 31 bp insertion sequences integrated into the plasmid (figure 1, p 899). At the time of the invention it would have been obvious to include the transposase encoding sequences taught by Rio et al in the vector of Clough or to provide the transposase encoding sequences in a separate vector with a reasonable expectation of success. An artisan of skill would have been motivated to include transposase coding sequences in the expression vector because this would eliminate the administration of the protein to a cell separately and introduce this vector into a mouse embryo because Clough teaches that this system provides a means of enhancing the transfer of genes into mammalian embryos.

Thus claims 27-34, are anticipated.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630

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